Poster Networking Sessions

PB1544 - Human Gene Therapy for The Inherited Platelet Bleeding Disorder Glanzmann Thrombasthenia

Return to schedule page

Tuesday, Jun 24, 2025 1:45 PM - 2:45 PM EDT

Location: Exhibition Hall D & E, Walter E. Washington Convention Center

Session Code: 12713

Session Code 2: PB1544

Aims	To develop a clinically relevant strategy for efficient modification of human CD34+cells with lentivector "GTalpha2B" encoding the *ITGA2B* gene promoter driving expression of integrin αIIb in progeny megakaryocytes *ex vivo* that will support testing in patients.
Background	Glanzmann Thrombasthenia (GT) results from integrin αIIbß3 defects that prevent platelet aggregation causing lifelong mucocutaneous bleeding leading to morbidity and mortality. Uncontrolled bleeding is commonly treated with platelet transfusions, antifibrinolytics, and rFVIIa. Although, there is no adequate cure for GT. Our previous preclinical studies showed proof-of-principle that hematopoietic stem cells (HSC) modified with transgenes encoding αIIbß3 provide safe and effective long-term hemostasis in GT animal models. This suggests feasibility for genetic therapy for GT patients.
Conclusion(s)	The data show that our GTalpha2B gene transfer strategy can provide effective modification of human Dami, CD34+cells and progeny megakaryocytes with comparable efficiency to canine GT HSC. This outcome indicates further testing of GTalpha2B on patient CD34+cells *ex vivo* may enable a first-in-human study for GT.
Methods	Studies were designed to investigate if GTalpha2B gene transfer causes significant gene marking and expression in human promegakaryocyte cell line (Dami), and megakaryocyte progeny of human (non-GT) CD34+cells comparable to canine GT HSC. Immunocytometry will confirm if sufficient αIIbβ3 receptors form on human megakaryocytes comparable to canine samples.
Results	The GTalpha2B proviral sequence assembled *de novo* as expected within transduced Dami genomic DNA. Immunocytometry revealed that transduced Dami displayed αIIbβ3 at an increased mean fluorescence intensity (MFI) representing ~2x normal receptor levels over controls. Interestingly, GTalpha2B-treated normal human CD34+cells at a vector copy number of ~0.5/cell had 1.5x increased levels of αIIbβ3 on megakaryocytes *in vitro* consistent with ~2x increased αIIbβ3 levels on megakaryocytes of transduced canine GT HSC. Tissue-cultured megakaryocytes were comparable in number for each sample indicating that GTalpha2B did not affect viability. Analysis of gene insertion and αIIbβ3 functionality are ongoing.

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